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CONCISE REPORTS

Urinary Excretion of β_2-Microglobulin Predicts Renal Outcome in Patients with Idiopathic Membranous Nephropathy[1]

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(J. Am. Soc. Nephrol. 1995; 6:1666–1669)

ABSTRACT

In patients with membranous nephropathy, treatment should be limited to those at risk for disease progression. Urinary β_2-microglobulin excretion was measured in 30 patients with membranous nephropathy, a nephrotic syndrome, and normal renal function (endogenous creatinine clearance > 80 mL/min), who were subsequently monitored for a median of 48 months. Renal function deteriorated in 11 of the 14 patients with a β_2-microglobulin excretion >500 ng/min and in only 2 of the 16 patients with a β_2-microglobulin excretion ≤500 ng/min ($P < 0.001$). The measurement of urinary β_2-microglobulin excretion thus contributes to the identification of patients with membranous nephropathy at high risk for developing renal insufficiency and may provide guidance for early immunosuppressive treatment.

Key Words: *Membranous nephropathy, β_2 microglobulin, renal insufficiency*

Membranous nephropathy is the most common cause of nephrotic syndrome in adults. Its natural course is quite variable. The majority of patients will retain normal renal function with a partial or complete remission of proteinuria (1,2). However, in about a quarter of the patients, renal insufficiency will develop. If renal insufficiency occurs, the majority shows progression within 2.5 yr after renal biopsy (2). Treatment with immunosuppressive drugs has been advocated for all patients with membranous nephropathy (3,4), but such a strategy seems not justified because it would expose many patients unnecessarily to these potentially toxic drugs. Immunosuppressive therapy should be limited to patients who are at the greatest risk for disease progression (5). Identification of patient characteristics that are associated with poor outcome would allow "tailor-made" treatment. Several prognostic factors have been associated with the progression to renal insufficiency, including age (1), male sex (6), proteinuria (7), and HLA-DR linkage (8). Deteriorating renal function at the time of diagnosis is also associated with a higher risk of the development of ESRD (1,2). Although some authors have found that morphologic staging of glomerular alterations could give a clue of renal outcome (9), most have found it an unreliable predictor (2,10–12). Better correlations with renal outcome have been reported for the severity of tubulointerstitial changes (13). Urinary β_2-microglobulin excretion, a sensitive marker of proximal tubular function, may reflect the presence of incipient tubulointerstitial damage. These slight tubulointerstitial alterations can easily be missed in renal biopsies. In this study, we have evaluated the role of urinary β_2-microglobulin excretion as a predictor for disease progression in patients with membranous nephropathy who have a nephrotic syndrome and normal renal function.

METHODS

Patients with a biopsy-proven membranous nephropathy, a nephrotic syndrome (*i.e.*, urinary protein excretion exceeding 3.5 g/day and/or a serum albumin ≤ 25 g/L), and normal renal function were eligible for the study. Until 1989, patients were treated with alternate-day steroids (14). Our data did not support any beneficial effects of alternate-day prednisone, which is in agreement with more recent studies (15,16). Since 1989, patients were randomized for treatment with prednisone on alternate days or only supportive treatment. No difference was noted in renal outcome. Because the patients were studied before treatment and prospectively monitored afterwards, it allowed us to evaluate the value of urinary β_2-microglobulin excretion in predicting the deterioration of renal function. Patients were monitored for at least 12 months after the measurement of urinary β_2-microglobulin excretion. Deterioration of renal function was defined as a sustained rise of the serum creatinine level of at least 25% on repeated measurements within 3 months (1 patient) or a doubling of the serum creatinine level at any time interval (12 patients). Dehydration and renal vein thrombosis as a cause of rise in the serum creatinine level were excluded on clinical grounds. When a patient had deterioration of renal function, immunosuppressive treatment with either chlorambucil or cyclophosphamide was started (17,18). During the collection of urine for the determination of β_2-microglobulin, sodium bicarbonate was administered orally to ensure a pH above

[1] Received January 26, 1995. Accepted July 27, 1995.

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1046-6673/0606-1666$03.00/0
Journal of the American Society of Nephrology
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6.0. The serum albumin level was measured by scattered light turbidity in a nephelometer. The remainder of the laboratory investigations were done by standard laboratory techniques.

The Toronto Glomerulonephritis Registry has developed probability modeling to predict the likelihood that a patient with membranous nephropathy will progress to chronic renal insufficiency (19). In this model, the risk of progressing to chronic renal insufficiency is increased when severe proteinuria persists. Patients with a urinary protein excretion of more than 8 g/day for more than 6 months had a 66% chance of progressing to chronic renal insufficiency, compared with a baseline probability of 26% in unselected patients. Patients with a proteinuria of more than 6 g/day for 9 months or more had a chance of 55%, and those with a proteinuria of more than 4 g for more than 18 months had a chance of 47% of progressing to chronic renal insufficiency. We compared the sensitivity and specificity of the above-mentioned model of persistent proteinuria with β_2-microglobulin excretion and serum albumin levels in predicting renal insufficiency in our patients. The unpaired t test was used to compare continuous variables between the groups of patients with stable and deteriorating renal function during follow-up. In case of nonparametric distributions, the Mann-Whitney U test was used. χ^2 techniques were used to compare the dichotomized variables. The method of Kaplan and Meier was used in the survival analysis. Values are given as means (± SD) or medians (range).

RESULTS

The patients were studied a median of 2 months (range, 0–140 months) after renal biopsy. The majority of patients ($N = 26$) were studied within the first year after biopsy. All patients had a normal renal function with a creatinine clearance of 120 ± 28 mL/min (mean ± SD; range, 85 to 210 mL/min) and had a nephrotic syndrome with a proteinuria of 10.1 ± 5.4 g/day (range, 5.1–28.5 g/day) and a serum albumin of 21.6 ± 6.2 g/L (range, 7.4–32.0 g/L). At the end of follow-up (median, 48 months; range, 12–132 months) 2 patients had died after 12 and 60 months, with normal renal function, and 13 patients had a deterioration of renal function. When comparing the group with stable renal function (Group 1, $N = 17$) with the group with deteriorating renal function (Group 2, $N = 13$), no significant differences were found in sex, age, renal function, or length of follow-up after the study (Table 1). At the start of the study, eight patients in Group 1 (stable renal function) and six patients in Group 2 (deteriorating renal function) were treated with diuretics. Three patients of Group 1 and four patients in Group 2 were treated with additional antihypertensive drugs. Blood pressure values at this time were not statistically different (Table 1). At 1 yr, at a time that renal function already was decreased in the majority of Group 2 patients, 10 patients in Group 1 and 8 in Group 2 were treated with antihypertensive drugs. At this time, blood pressure was numerically higher in Group 2 patients, although the difference did not reach statistical significance (Group 1 median, 135/79 mm Hg; range, 108–180/58–104; Group 2 median, 140/88 mm Hg; range, 110–176/75 110; $P = 0.25$). The patients with renal insufficiency during follow-up had more proteinuria and a lower serum albumin level (Table 1). Also, a significant difference between the two groups was seen with respect to the urinary excretion of β_2-microglobulin (Table 1, Figure 1). Overall, we found a weak correlation between serum albumin levels and the logarithm of urinary β_2-microglobulin excretion ($r = -0.39$, $P = 0.04$). We evaluated three levels of serum albumin, three levels of urinary excretion of β_2-microglobulin, and three models of persistent proteinuria to select optimal predictive characteristics of subsequent renal insufficiency (Table 2). A urinary β_2-microglobulin excretion of 500 ng/min and Model 1 of persistent proteinuria (*i.e.*, proteinuria of more

TABLE 1. Characteristics of the two patient groups at the start of the study and at follow-up[a]

Parameter	Stable Renal Function ($N = 17$)	Deteriorating Renal Function ($N = 13$)
Sex (Male/Female)	12/5	12/1
Age (yr) at Biopsy	48 ± 8	40 ± 13
Interval From Biopsy to Study Entry (month)	2 (0–140)	2 (0–87)
Laboratory Data at Study Entry		
Serum creatinine (μmol/L)	90 ± 16	102 ± 26
Endogenous creatinine clearance (mL/min)	116 ± 23	124 ± 35
Proteinuria (g/day)	8.4 ± 3.9	12.2 ± 6.4[b]
Serum albumin (g/L)	23.4 ± 4.6	19.2 ± 7.4[b]
Urinary β_2-microglobulin excretion (ng/min)	249 (61 to 24,988)	2,806 (146 to 13,519)[c]
Blood pressure at Study Entry (mm Hg)	137/80 ± 16/10	148/84 ± 19/8
Follow-up (month)	50 ± 35	54 ± 27
Laboratory Data at Follow-Up		
Serum creatinine (μmol/L)	94 ± 18	481 ± 397
Serum albumin (g/L)	37 ± 8	34.4 ± 8.7

[a] Values are given as medians (range) or means ± SD.
[b] $P < 0.05$.
[c] $P < 0.01$.

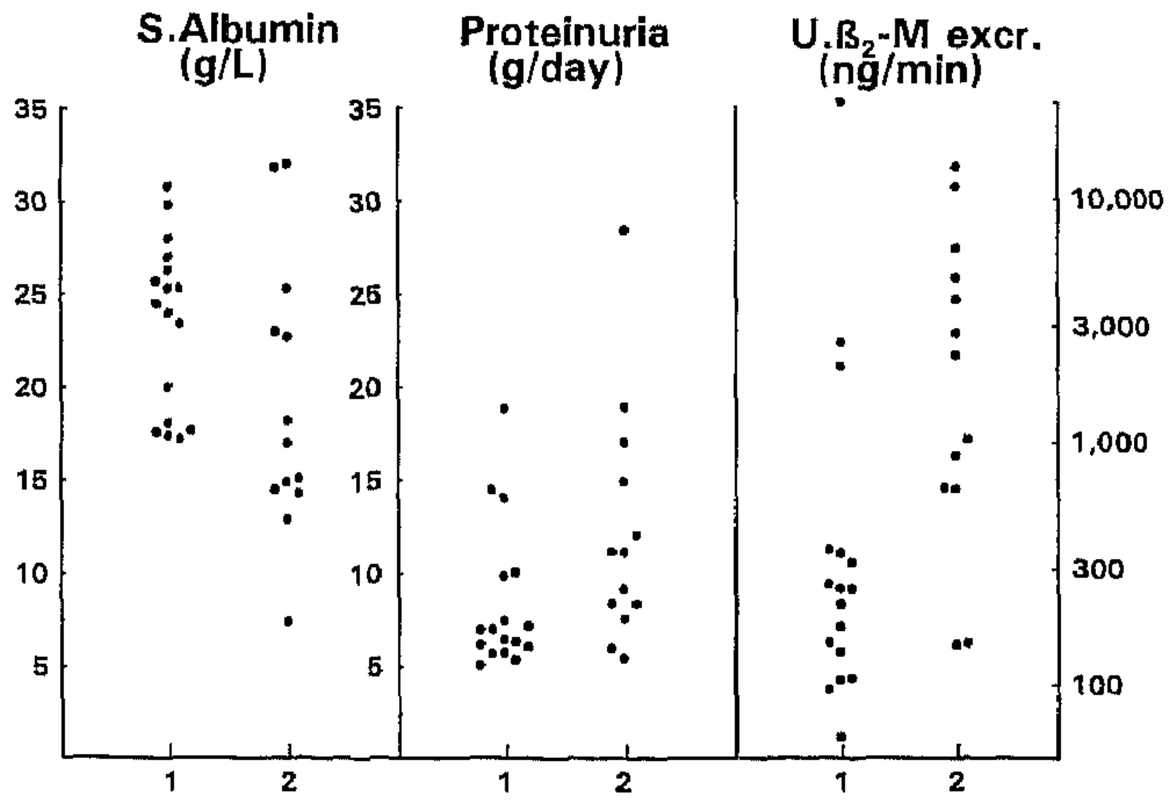

Figure 1. Scatter plot of values for serum (S.) albumin, proteinuria, and urinary β_2-microglobulin excretion (U.β_2-M excr.) at the start of the study. Group 1 represents patients with stable renal function; Group 2 represents patients with deteriorating renal function during follow-up.

TABLE 2. Test characteristics of different levels of β_2-microglobulin excretion, serum albumin, and the model of persistent proteinuria[a]

Parameter	PPV (%)	NPV (%)	SENS (%)	SPEC (%)
U.β_2-M Excr. >250 ng/min	61	83	85	59
U.β_2-M Excr. >500 ng/min	79	88	85	82
U.β_2-M Excr. >1,000 ng/min	73	74	62	82
Serum Albumin ≤15 g/L	100	68	39	100
Serum Albumin ≤20 g/L	62	71	62	71
Serum Albumin ≤25 g/L	53	73	77	47
Persistent Proteinuria 1[b]	73	81	73	81
Persistent Proteinuria 2[b]	71	92	91	75
Persistent Proteinuria 3[b]	67	92	91	69

[a] Explanation of abbreviations: PPV, positive predictive value; NPV, negative predictive value; SENS, sensitivity; SPEC, specificity; U.β_2-M excr. urinary β_2-microglobulin excretion.
[b] The model of persistent proteinuria. Model 1, proteinuria ≥8 g/day for more than 6 months; Model 2, proteinuria ≥6 g/day for more than 9 months; Model 3, proteinuria ≥4 g/day for more than 18 months.

than 8 g for more than 6 months) appeared to be the best predictors of renal insufficiency. Renal function deteriorated in 11 of the 14 patients with a β_2-microglobulin excretion >500 ng/min and in only 2 of the 16 patients with a β_2-microglobulin excretion ≤500 ng/min ($P < 0.001$; Figure 2). Our results could have been biased because in our study, we included four patients who were studied more than 1 yr after renal biopsy and one patient who was treated with cyclophosphamide because of rapid deterioration of renal function at a time when his serum creatinine level had not yet doubled. Therefore, the calculations were repeated after the exclusion of the five above-mentioned patients. This analysis yielded similar results. Group 1 comprised 15 patients (10 men, 5 women) who were studied 2 months (range, 0–8 months) after renal

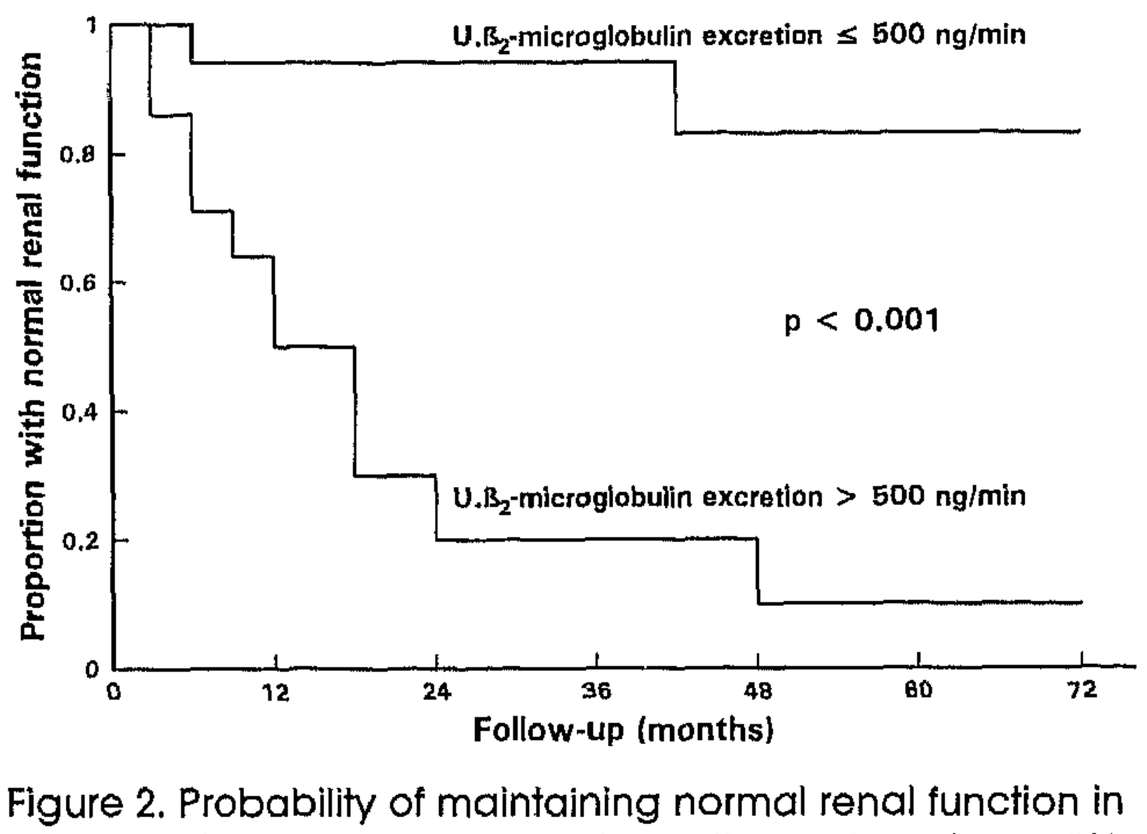

Figure 2. Probability of maintaining normal renal function in patients with membranous nephropathy and a urinary (U.) β_2-microglobulin excretion ≤ or >500 ng/min.

biopsy and were monitored for 43 months (range, 12–132 months). Mean age was 47 ± 8 yr, creatinine clearance was 115 ± 23 mL/min, proteinuria was 8.5 ± 4.1 g/24 h, serum albumin level was 23.1 ± 4.7 g/L, and urinary β_2-microglobulin excretion was 215 ng/min (range, 61–24,988 ng/min). Group 2 comprised 10 patients (all men) who were studied for 1 month (range, 0–11 months) after renal biopsy and were monitored for 48 months (range, 12–84 months). Mean age was 39 ± 14 yr, creatinine clearance was 135 ± 34 mL/min, proteinuria was 10.8 ± 3.9 g/24 h ($P > 0.20$ compared with Group 1), serum albumin level was 17.5 ± 6.8 g/L ($P = 0.16$ compared with Group 1), and a urinary β_2-microglobulin excretion was 1,645 ng/min (range, 146–6,241 ng/min; $P = 0.01$ compared with Group 1). Renal function deteriorated in 8 of the 10 patients with a β_2-microglobulin excretion >500 ng/min and in only 2 of the 15 patients with a β_2-microglobulin excretion ≤500 ng/min ($P < 0.005$).

Of all patients, 13 had a deteriorating renal function, of whom 7 were treated with chlorambucil and prednisone. After treatment, renal function improved or remained stable in four of these patients. Of the six patients not treated with chlorambucil and prednisone, four developed ESRD and two had a further deterioration of renal function. Laboratory parameters at follow-up are given in Table 1.

DISCUSSION

Defining the optimal treatment strategy for patients with idiopathic membranous nephropathy is still a matter of debate (4,5,20). Although studies have reported promising results from the use of immunosuppressive drugs, investigators disagree on the optimal timing of treatment start. Treatment could be limited to patients with membranous nephropathy and renal insufficiency. These patients almost certainly progress to ESRD unless treatment is instituted (1,2,17). However, treatment efficacy may be less in

such patients and the glomerular and tubular damage may be permanent. Alternatively, treatment could be instituted in all patients with membranous nephropathy and a nephrotic syndrome. Although such a strategy has indeed been advocated on the basis of the results of randomized studies (4), opponents rightly argue that this would unjustifiably expose up to three-quarters of patients to potentially toxic immunosuppressive drugs (5,20). In order to be able to limit immunosuppressive therapy to those patients at risk for the development of renal insufficiency, it is necessary to identify such patients at risk at a stage before renal insufficiency becomes manifest. In the last two decades, several prognostic factors, such as age, sex, HLA-DR, and glomerular and tubulointerstitial injury, have emerged. The sensitivity and specificity of these factors are not defined, however, and may be quite low. The Toronto Glomerulonephritis Registry has made an attempt to quantify the risk of developing renal insufficiency by using different cutoff levels of proteinuria in a selected time interval (19). To date, this is the most useful model to identify patients at risk. However, it requires at least 6 to 18 months of follow-up to identify those patients. We have evaluated the predictive value of measuring urinary β_2-microglobulin excretion in patients with membranous nephropathy and a nephrotic syndrome. All patients were studied at a time that renal function was still normal. Our data suggest that the measurement of urinary β_2-microglobulin excretion is an easy tool for the early identification of patients at risk for the development of renal insufficiency. The findings are in keeping with the notion that urinary β_2-microglobulin excretion reflects tubulointerstitial injury and that the extent of tubulointerstitial injury determines prognosis in membranous nephropathy (13). It is important to note that the degradation of urinary β_2-microglobulin occurs in acid urine. Therefore, the urine collections should be carried out under adequate treatment with sodium bicarbonate to ensure a urinary pH above 6.0. The results of our study should be confirmed in a more extensive study. We propose to measure β_2-microglobulin excretion in the urine in future studies to identify patients with membranous nephropathy and normal renal function at the highest risk of the deterioration of renal function. This will allow for the earlier treatment of those patients at risk.

ACKNOWLEDGMENTS

L.J.M. Reichert is supported by a grant from the Netherlands Foundation of Scientific Research (NWO grant 0703/716-111). We thank Drs. J. Jordans, Ziekenhuis de Stadsmaten, Enschede; R. Go, Canisius Wilhelmina Ziekenhuis, Nijmegen; H. van Roermund, St. Franciscusziekenhuis, Roosendaal; G. Schrijver, Rode Kruis Ziekenhuis, Beverwijk; M. den Hartog, Ziekenhuis Gelderse vallei, Wageningen; V. Verstappen, St. Maartensgasthuis, Venlo; P. Hillen, Elisabeth Ziekenhuis, Tilburg; F. van Liebergen and J. Jansen, Groot Ziekengasthuis, Den Bosch; P. Gerlag and A. van den Wall Bake, St. Joseph Ziekenhuis, Veldhoven, for participation in this study. We thank Dr. A.J. Hoitsma for statistical assistance.

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